Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Regadenoson (new therapeutic indication: measurement of the fractional flow reserve)

of 15 August 2019

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient regadenoson was first placed on the market on 15 April 2011.

On 23 January 2019, regadenoson received marketing authorisation for the new therapeutic indication: “for use in adults as a pharmacological stress agent for the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography when repeated FFR measurements are not anticipated”.

In a letter dated 11 December 2018, the pharmaceutical company was informed that a benefit assessment in accordance with Chapter 5, Section 1, paragraph 2, number 2 VerfO is planned for the extension of the marketing authorisation of regadenoson for the measurement of myocardial FFR because this is a new therapeutic indication for a medicinal product with a new active ingredient. The pharmaceutical company was requested to submit a dossier on the active ingredient regadenoson in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the Federal Joint Committee (G-BA) in good time (i.e. within four weeks of marketing authorisation of the new therapeutic indication or notification of approval for a new therapeutic indication.)

The pharmaceutical company did not submit a complete dossier at the relevant time (within four weeks of marketing authorisation) according to Chapter 5, Section 8, paragraph 1 in conjunction with Section 11, paragraph 1, sentence 1 VerfO.

The pharmaceutical company has therefore not submitted the necessary evidence for the benefit assessment according to Section 35a SGB V to the G-BA at the relevant time despite being requested to do so. The legal consequence of Section 35a, paragraph 1, sentence 5 SGB V is that an additional benefit is not proven.

The inclusion of regadenoson in the scope of the benefit assessment according to Section 35a SGB V does not prevent regadenoson from being used within the scope of the investigation or treatment method “Measurement of the myocardial fractional flow reserve (FFR)”. After the G-BA has recognised this method according to Section 135 paragraph 1 SGB V and it is included as a billable service in the uniform valuation standard, the method reservation no longer exists in this respect. In addition, an assessment in accordance with Section 135, paragraph 1 SGB V in accordance with Chapter 1 Section 5 VerfO was carried out exclusively for the method of myocardial fractional flow reserve in coronary heart disease but not for the medicinal product regadenoson. Finally, it is also not evident that the combination of regadenoson and the “measurement of myocardial fractional flow reserve (FFR)” is based on a theoretical-scientific concept that differs from the performance billable according to EBM. In particular, it cannot be inferred from the product information that the use of the new active ingredient requires the performance of new procedural steps in the course of a “measurement of the myocardial fractional flow reserve (FFR)” that go beyond the recognised methodology according to the EBM and could, from this point of view, necessitate an examination according to Section 135, paragraph 1 SGB V. Nor does the nature of the application suggest that a new methodological concept underlies the use of regadenoson as part of a “measurement of myocardial fractional flow reserve (FFR)”. According to product information, the drug is injected into the patient’s body by means of an injection.

By resolution of 17 November 2017, which entered into force on 1 February 2018, the measurement of the myocardial fractional flow reserve in coronary heart disease was included in Annex I: “Recognised investigation or treatment methods” of the G-BA guideline on investigation and treatment methods of SHI-accredited physicians’ care. The assessment in accordance with Section 135, paragraph 1 SGB V in conjunction with Chapter 1, Section 5 VerfO did not include regadenoson.

Even if EBM number 34298 in conjunction with EBM number 40301, which is intended for the FFR, contains all material costs and thus also the optional service content of medicinal vasodilatation, this does not prevent a benefit assessment of regadenoson according to Section 35a SGB V. This is because Rapiscan®, as a reimbursable medicinal product with a new active ingredient and with a new therapeutic indication, is subject to the scope of application according to Section 35a SGB V in conjunction with Chapter 5, Section 1, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA. On this basis, a cost regulation on medicinal products with new active ingredients in the EBM according to Section 87, paragraph 2 SGB V, which are used within the framework of methods according to Section 135, paragraph

1 SGB V, leaves the regulation in Section 130b, paragraph 1 SGB V for the agreement of a reimbursement amount for medicinal product assessed for use according to Section 35a SGB V unaffected. Thus, the benefit assessment of Rapiscan® can be used as a basis for a reimbursement amount according to Section 130b SGB V in a purposeful manner.

In its benefit assessment, the G-BA made findings on the appropriate comparator therapy, the number of patients in the target population, the requirements for a quality-assured application, and treatment costs. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 3 June 2019, thus initiating the written statement procedure.

In addition, an oral hearing was held.

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of regadenoson (Rapiscan®) in accordance with the product information

Rapiscan® is a selective coronary vasodilator for use in adults as a pharmacological stress agent for:

- […]
- the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography when repeated FFR measurements are not anticipated.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients in whom the fractional flow reserve (FFR) of a single coronary artery stenosis is measured using a pharmacological stress agent during invasive coronary angiography when repeated FFR measurements are not anticipated

Pharmacological stress agent according to the physician's instructions

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. No other medicinal products are authorised in the therapeutic indication other than the medicinal product to be evaluated.

On 2. There is no non-medicinal comparator therapy in the therapeutic indication

On 3. There is a resolution of 17 November 2017 amending the directive Methods of contracted medical care (MVV-RL), and the following point has been added to Annex I (Methods that may be provided as contracted medical care at the expense of health insurance funds: "22. Measurement of myocardial fractional flow reserve in coronary heart disease". In this resolution and also in the final report of the IQWiG Measurement of myocardial fractional flow reserve (FFR) in coronary artery disease, no medicinal products for myocardial stress agent are named.

On 4. The generally accepted state of medical knowledge was determined by an evidence search. No medicinal products are approved for the therapeutic indication. In systematic reviews and guidelines, medicinal vasodilatation for stress induction with adenosine or nitroprusside is recommended; however, these are not permitted in this therapeutic indication. Therefore, a pharmacological stress agent is determined as an appropriate comparator therapy according to the physician's instructions. The active ingredients adenosine or nitroprusside can be regarded as suitable comparators.

The measurement of myocardial fractional flow reserve can be performed with or without medicinal vasodilatation according to MVV-RL.

However, the present therapeutic indication of Rapiscan® ("…selective coronary vasodilator for use in adults as a pharmacological stress agent for…") explicitly refers to the myocardial fractional flow reserve with medicinal vasodilatation so that only this option is considered in determining the appropriate comparator therapy.

From the suitability as a comparator, it is not possible to draw any conclusions about its usefulness in the form of application in the standard care of insured persons in the SHI system that exceeds the approval limits. Such an assessment is reserved for the decision according to Section 35c SGB V.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of regadenoson is assessed as follows:

The additional benefit is deemed not to have been proven.

Justification:

The pharmaceutical company did not submit a complete dossier at the relevant time. In accordance with Section 35a, paragraph 1, sentence 5 SGB V, this has the consequence that no assessment is made as to whether the active ingredient regadenoson has an additional benefit, no additional benefit, or a lesser benefit compared with the appropriate comparator therapy in the therapeutic indication measurement of FFR and that the additional benefit of regadenoson in relation to the appropriate comparator therapy is regarded as not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient regadenoson. The new therapeutic indication of regadenoson to be evaluated is as follows: “Rapiscan® is a selective coronary vasodilator for use in adults as a pharmacological stress agent for the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography when repeated FFR measurements are not anticipated”.

The G-BA determined a pharmacological stress agent in accordance with the physician’s instructions as an appropriate comparator therapy.
The pharmaceutical company did not submit a complete dossier at the relevant time. In accordance with Section 35a, paragraph 1, sentence 5 SGB V, this has the consequence that no assessment is made as to whether or to what extent there is an additional benefit for the active ingredient regadenoson in the therapeutic indication measurement of FFR compared with the appropriate comparator therapy. The additional benefit of regadenoson in relation to the appropriate comparator therapy is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The measurement of the myocardial fractional flow reserve may be performed as a service at the expense of the statutory health insurance for patients in whom

- coronary heart disease (CHD) is present
- there is an indication for coronary angiography
- the indication for coronary intervention is not clear because of the angiographic findings

In 2016, 897,941 coronary angiographies and 377,764 PCI were performed in Germany[1].

Assuming that all patients undergoing coronary angiography could not be clearly indicated for PCI, the maximum number of patients eligible for FFR should be based on the number of coronary angiographies performed.

This figure represents a clear overestimation; in the case of an indeterminable proportion of patients, the performance of an FFR is not indicated because the indication for the performance or non-performance of a PCI can already be clearly defined.

A lower limit of the number is not to be specified for the reasons mentioned above.

SHI target population

According to the Federal Health Monitoring, 86.5% of the population is covered by statutory health insurance.

This results in a maximum number of approx. 780,000 patients.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account.

Treatment with Rapiscan® may only take place in a medical facility where equipment is available for monitoring cardiac function and for cardiac resuscitation.

[1] Federal health monitoring information system, frequency of percutaneous coronary interventions (PCI), number of left ventricular catheterisation sites and left ventricular catheterisation investigations. Online http://www.gbe-bund.de [as access 14 May 2019]

The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Rapiscan® (active ingredient: regadenoson) at the following publicly accessible link (last access: 31 July 2019):

https://www.ema.europa.eu/documents/product-information/rapiscan-epar-product-information_en.pdf

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2019).

On the representation of the duration of treatment:

As a rule, a maximum of one FFR measurement per year and a single dose of the medicinal product to be evaluated (regadenoson) or the appropriate comparative therapy are assumed. Repeated use of regadenoson in the same session is not considered in the therapeutic indication "Measurement of FFR in invasive coronary angiography when repeated FFR measurements are not anticipated".

On the representation of the costs

The medicinal product to be evaluated, regadenoson (Rapiscan®), is not subject to the Pharmaceutical Price Ordinance. Thus, there is no manufacturer rebate for this medicinal product according to Section 130a SGB V. The costs of regadenoson are shown on the basis of the ex-factory price plus VAT.

For the cost presentation of the appropriate comparative therapy "pharmacological stress agent according to the physician's instructions", no information is given. The actual costs incurred by the health insurance funds in accordance with Section 4, paragraph 8, sentences 1 to 5 AM-NutzenV can only be stated to the extent that they can generally be prescribed to the detriment of the statutory health insurance funds according to the reimbursement principles in SGB V (laws, ordinances, guidelines of the G-BA). As a rule, medicinal products used off-label-use (e.g. adenosine) cannot be prescribed at the expense of the statutory health insurance funds because such regular reimbursement of costs presupposes a decision based on a positive recommendation according to Section 35c SGB V. For off-label use that is not regulated, the case law of the Federal Social Court on prescribability in individual cases remains unaffected.

The costs for the implementation of an FFR are incurred both on the part of the medicinal product to be evaluated and on the part of the appropriate comparator therapy and are therefore not shown in the cost breakdown.

Treatment period

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Regadenoson	1 x per angiography	1	1	1

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Appropriate comparator therapy				
Pharmacological stress agent according to the physician's instructions	no data available			

Usage and consumption:

Designation of the therapy	Dosage	Dosage/ patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Regadenoson	400 µg	400 µg	1 x 400 µg	1	1 × 400 µg
Appropriate comparator therapy					
Pharmacological stress agent according to the physician's instructions	no data available				

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Cost
Medicinal product to be assessed		
Regadenoson	1 injection solution	€ 64.26
Appropriate comparator therapy		
Pharmacological stress agent according to the physician's instructions	no data available	

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the usual expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 9 April 2019.

On 23 January 2019, regadenoson received marketing authorisation for the new therapeutic indication, measurement of the FFR. The pharmaceutical company did not submit a complete dossier within four weeks of marketing authorisation.

The G-BA prepared the benefit assessment.

The written statement procedure was initiated with the publication of the benefit assessment prepared by the G-BA on the G-BA website on 3 June 2019. The deadline for submitting written statements was 24 June 2019.

The oral hearing was held on 9 July 2019.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 August 2019, and the proposed resolution was approved.

At its session on 15 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	9 April 2019	Determination of the appropriate comparator therapy
Working group Section 35a	2 July 2019	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal product	9 July 2019	Conduct of the oral hearing
Working group Section 35a	16 July 2019 30 July 2019	Advice on the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG), evaluation of the written statement procedure
Subcommittee Medicinal product	6 August 2019	Concluding discussion of the proposed resolution
Plenum	15 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2019

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The chair

Prof Hecken